Primary Cutaneous Malignant Perivascular Epithelioïd Cell Tumor (PEComa): Case Report With Review of the Literature

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ABSTRACT: Perivascular epithelioïd cell tumor (PEComa) is a mesenchymal neoplasm with epithelioïd or spindled morphology with numerous thin-walled capillaries between tumor cells. They co-express markers of both melanocytic and smooth muscle differentiation. PEComas are rare, presenting in numerous anatomic sites including lung, kidney, liver, genitourinary tract, soft tissue, and skin. Primary cutaneous PEComas are very rare entity, and malignant ones are even more uncommon. Herein, we report the case of a 92-year-old female which was presenting with 7 cm exophytic, ulcerated, hemorrhagic nodular tumor, and rapidly growing for 8 months over the right thigh. On histologic examination, we found a dermal neoplasm formed by an atypical clear cell tumor with numerous branching capillaries between tumor cells. The mitotic count was found 6 mitotic figures/10 HPF. On immunohistochemistry, tumor cells co-expressed smooth muscle and melanocytic markers, CD10, and CD68. Based on these findings, the diagnosis of primary cutaneous malignant perivascular epithelioïd cell tumor (PEComa) was made. The large size (7 cm), the count of mitoses (6 mitotic figures/10 HPF), and the nuclear pleomorphism argued for malignancy. The absence of soft tissue or visceral localization argued for the cutaneous primitive origin. Adjuvant radiotherapy and targeted therapy with mTOR inhibitor (nab-sirolimus) was indicated. To the best of our knowledge, this is only the eighth case of a primary cutaneous malignant PEComa reported in the literature to date.

KEYWORDS: Primary, cutaneous malignancy, PEComa, immunohistochemistry, myo-melanocytic, perivascular epithelioïd cell, clear cell

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Introduction

Perivascular epithelioïd cell tumors (PEComas) are mesenchymal neoplasms composed of perivascular epithelioïd cells (PECs), distinctive epithelioïd cells that are often closely associated with blood vessels. These epithelioïd cells express both melanocytic and smooth muscle markers.[1] They are rare mesenchymal tumors, presenting in numerous anatomic sites including lung, kidney, liver, genitourinary tract, soft tissue, and skin. Primary cutaneous PEComas are very rare entity, and malignant ones are even more uncommon. This family of tumors includes renal angiomyolipoma, clear cell "sugar" cell tumor of the lung, lymphangioleiomyomatosis of the lung, clear cell myomelanocytic tumor of the falciform ligament, PEComas of somatic soft tissue, of visceral organ, and gynecologic tract.[2] In 2005, Folpe et al[3] proposed classifying PEComas as benign, uncertain malignant potential, or malignant, based on these criteria, tumor size ⩾5 cm, infiltrative growth pattern, high nuclear grade, necrosis, mitotic count up to 1/50 HPF, and aggressive clinical behavior. Therefore, A benign PEComa would have none of thfan aggressive skin malignancy.

Case Presentation

A 92-year-old female with no significant medical history, coming with a 7 cm exophytic, ulcerated, hemorrhagic nodular tumor rapidly growing for 8 months over the right thigh (Figure 1a and b). Magnetic resonance imaging showed budding cutaneous mass, extra-aponeurotic, located at the internal face of the right thigh, contrast enhancing intensely, and heterogeneously after injection of contrast product, it measured 7 cm × 5.5 cm × 5 cm. This was clinically suggestive of melanoma, squamous cell carcinoma, or sarcoma. A biopsy have been performed and sent to us. Histological examination after 10% buffered formalin fixation, impregnation, and block paraffin embedding, showed a dermal, and subcutaneous neoplasm with irregular nests and nodules, numerous branching capillaries were noted between tumor cells (Figure 2). Cells had abundant clear cytoplasm and enlarged polymorphic and vesicular nuclei with prominent nucleoli (Figure 3). The mitotic count was found 6 mitotic figures/10 HPF with atypical mitoses. There was no necrosis or vascular invasion. On immunohistochemistry, tumor cells co-expressed smooth muscle, and

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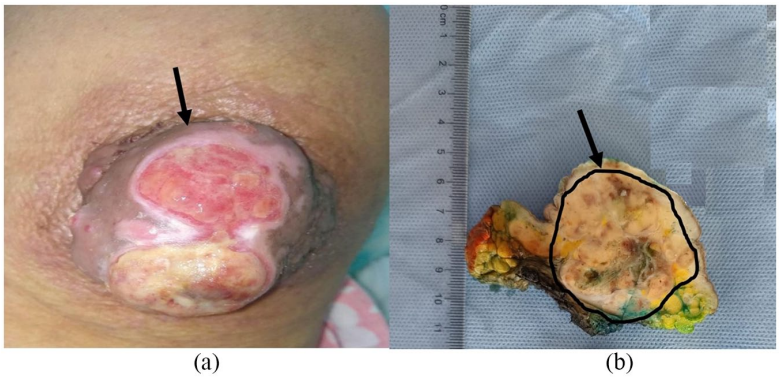

(a) (b)

Figure 1. (a) Clinical feature: exophytic, ulcerated, hemorrhagic nodular tumor of 7 cm, over the right thigh (arrow). (b) Macroscopically, dermo-hypodermic tumor, multinodular, whitish with hemorrhagic areas (circle).

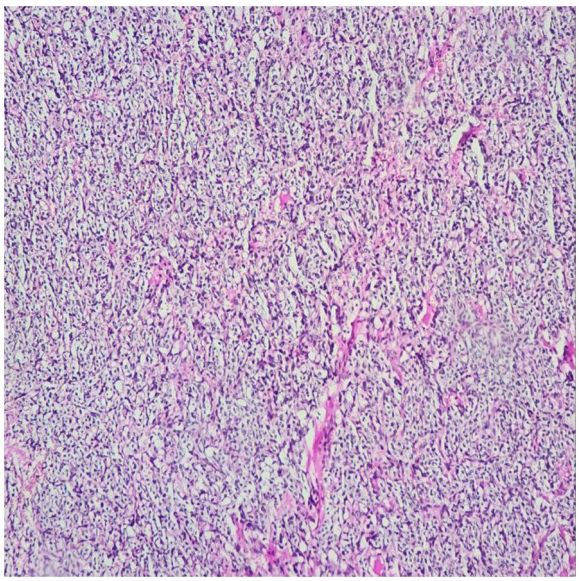

Figure 2. Tumor section, sheets of clear cells with numerous branching capillaries between tumor cells (hematoxylin and eosin stain ×100).

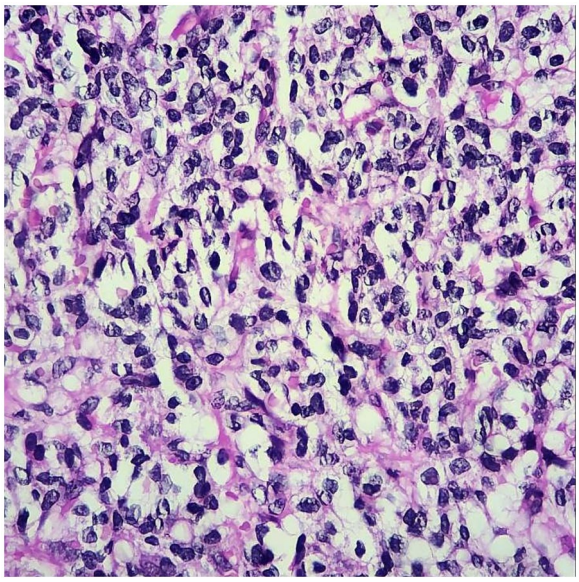

Figure 3. Higher magnification shows there are cellular atypia and atypical mitotic figures (hematoxylin and eosin stain ×400).

melanic markers, they are positive for Melan-*A* (Figure 4a), and smooth muscle actin (SMA; Figure 4b), they also expressed vimentin, CD10 (Figure 4c), and CD68. They were negative for epithelial markers (CK AE1/AE3, CK 7, CK20, EMA, P63), neuroendocrine markers (synaptophysin, chromogranin *A*), other muscle markers (Desmin, H-caldesmon), vascular markers (CD34, CD31), other melanin markers (PS100, HMB45), CD45, TFE3, and for myogenin. It should be noted that the immunostaining by CD34 highlighted the numerous branching capillaries between tumor cells (Figure 4d).

Based on histological and immunohistochemical features, the diagnosis of primary cutaneous malignant perivascular epithelioïd cell tumor (PEComa) was made. The large size (7 cm), the count of mitoses (6 mitotic figures/10 HPF), and the nuclear pleomorphism argued for malignancy. The absence of soft tissue or visceral localization argued for the cutaneous primitive origin.

Discussion

To date and to the best of our knowledge, this is only the eighth case of a primary cutaneous malignant perivascular epithelioïd cell tumor (PEComa) reported in the literature. We have realized a literature review using PubMed/Medline, Scopus, and Web of Science databases, with the search terms "PEComa, malignant, immunohistochemistry, perivascular epithelioïd cell, primary." On literature review, we found 68 cases of cutaneous PEComa including 59 benign cases, 7 malignant cases, and 2 cases of skin metastasis of primary uterine and adrenal gland PEComas. The first case was published by Calder in 2007, the second one was published in 2013 by Greveling as an abstract, then a third case was reported in 2017 by Haiges, a fourth case reported in 2021 by Cole and finally, 3 cases were published in 2022 separately by Cohen, Cornell, and Neumann. We summarized all clinical, histological, and immunohistochemical features of these cases including our current case in Tables 1 to 3.

Through the reported cases of primary cutaneous malignant PEComas, we had not noted a predilection of sex with a sex ratio of 1 (4 women/4 men). The mean age of patients was 56 years. Clinical presentation was predominated by a

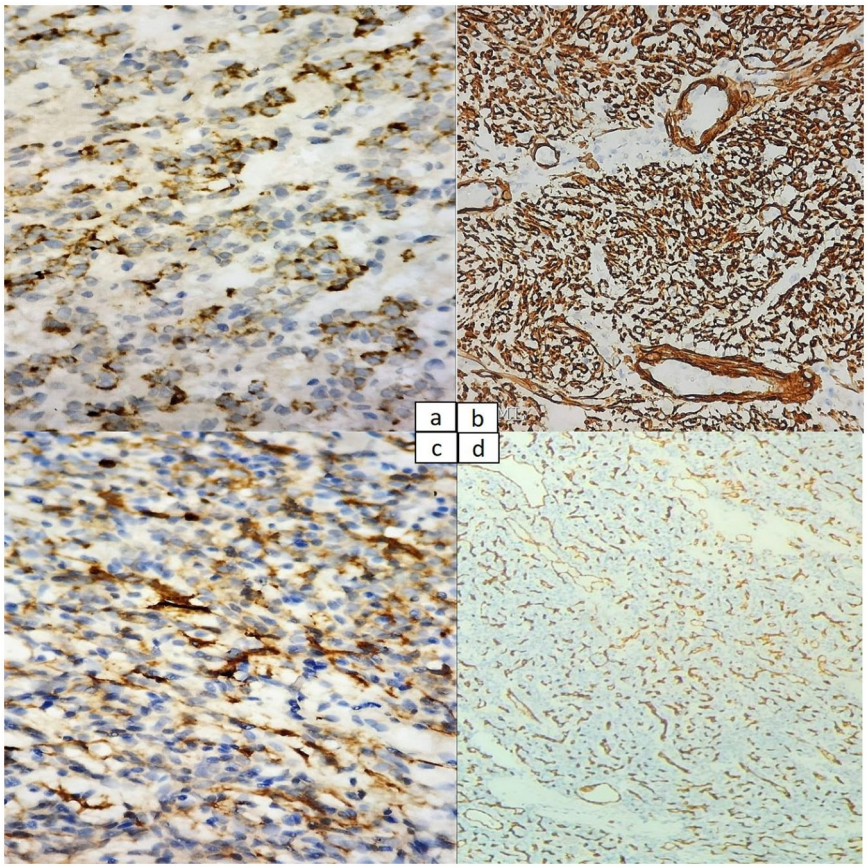

Figure 4. Immunohistochemical staining (a) cytoplasmic positive staining of Melan *A* (×400) (b) membranous and cytoplasmic positive staining of smooth muscle actin (SMA) (×400), (c) membranous positive staining of CD 10 (×400). (d) Positive staining of CD34 highlighting numerous thin-walled capillaries between tumor cells (×100).

growing, exophytic, and nodular tumor. Extremities were the site the most found on this review. The mean size was 40 mm (10-120 mm).

On histologic examination, all these reported tumors involved the dermis at least in part without connection to the epidermis, had infiltrating growth pattern and were characterizing by nodules, fascicles, and nests of epithelioïd or spindled cells. The cells had a clear or granular, eosinophilic cytoplasm. The nuclei were round or oval vesicular with a nucleolus. A ramifying network of capillaries between cells was noted. Mitotic count was ranging from 2 to up to 22 per 10 HPF with atypical mitoses in 3/8 cases. Necrosis was found in 1/8 case, ulceration found in 3/8 case, and no vascular invasion was noted.

Histologically, PEComa should be differentiated from any skin tumor with a clear cell change. This includes metastatic clear cell renal carcinoma, sebaceous carcinoma, clear-cell sarcoma, balloon-cell melanoma, balloon-cell nevi, clear cell hidradenoma, clear cell xanthoma, and the list is long.[11] For a precise diagnosis, a wide immunohistochemical analysis with a panel of multiple antibodies is required.

As previously reported, PEComas have characterized by co-expression of at least 1 melanocytic marker (HMB-45, Melan *A*, MiTF, tyrosinase) and 1 smooth muscle marker (SMA, Desmin, Hcaldesmone), while epithelial markers, neuroendocrine markers, SOX10 were never expressed. HMB-45 has seemed the most sensitive, it was positive in 6/8 cases (Table 3). On the other hand, it has noted that the smooth muscle markers had a lower rate of positivity in the primary cutaneous PEComas. Others non-specific markers which found positive in primary cutaneous PEComas were CD10 in 100% (4/4) tested cases), CD68 in 100% (3/3) tested cases) (Table 3). Usually, immunohistochemical CD10 positivity has been often allied to cutaneous metastases of clear cell renal carcinoma, however, 2 authors[12,13] had reported 3 cases and 5 cases of CD10-positive cutaneous PEComa, respectively, as well as our case was also CD10 positive.

In a recent publication,[14] the authors had tested the usefulness of the anti-PRAME antibody in the diagnosis of tumors with melanocytic differentiation. They had found a positivity of PRAME in a single case of PEComa among the 9 cases tested, then they concluded in this work that immunostaining for PRAME may be useful to support diagnosis of melanoma in the setting of difficult dermal melanocytic neoplasms and other epithelioïd neoplasms with melanocytic differentiation as PEComa.[14]

In contrast to systemic PEComa, TFE3 positivity had not observed in the 17 primary skin PEComas, reported by

Table 1. Clinical features of reported primary cutaneous malignant PEComa cases.

CASE	REFERENCE	YEAR	AGE (YEAR)	SEX	HISTORY	LOCATION	SIZE (MM)	CLINICAL FEATURE	CLINICAL DIAGNOSIS	TREATEMENT	FOLLOW-UP	RECURRENCE
1	Calder et al[4]	2008	76	male	melanoma	scalp	16	nodule	Pilar cyst	excision	NA	NA
2	Greveling et al[5]	2013	44	male	NA	Left cheek	10	Rapidly growing painless nodule	Cyst	excision	24 mo	NED
3	Haiges et al[6]	2017	41	Female	Pregnancy	back of the left thigh	35	indolent, slowly growing dermatofibroma-like tumor	dermtofibroma	excision	20 mo	NED
4	Cole et al[7]	2021	42	Female	NA	Right shoulder	35	painful erythematous firm nodule	NA	excision + radiotherapy	10 mo	NED
5	Cornell et al[9]	2022	77	Female	Multiple cutaneous SCC	Right shin	20	large, pink, exophytic tumor	NA	excision	6 mo	NED
6	Cohen et al[8]	2022	43	male	family history of skin cancer	Distal left forearm	10	exophytic nodular tumor	keratoacanthoma	excision	6 mo	NED
7	Neumann et al[10]	2022	34	male	Crohn disaese	Right shoulder	120	enlarging, raised, rounded mass	Abscess	excision	NA	NED
8	Present case	2023	92	Female	None	Right thigh	70	exophytic, ulcerated, hemorrhagic nodular tumor rapidly growing	Melanoma, SCC, Sarcoma	excision + radiotherapy + nab-sirolimus (mTOR inhibitor)	6 mo	NED

Abbreviation: NA, not available; NED, no evidence of disease; SCC, squamous cell carcinoma.

Table 2. Histopathological features of reported primary cutaneous malignant PEComa cases.

CASE	REFERENCE	YEAR	ARCHITECTURE	CONNECTION TO THE EPIDERMIS	ACN	MITOSIS	ATYPICAL MITOSIS	ULCERATION	NECROSIS	VASCULAR INVASION
1	Calder et al[4]	2008	nidus of clear cells + ramifying network of capillaries	No	Yes	2/10 HFP	NO	NO	NO	NO
2	Greveling et al[5]	2013	Irregular nests with epithelioid and spindle cells, presence of branching capillaries . Granular cells containing enlarged polymorphic nuclei with prominent nucleoli.	No	Yes	5/10HFP	NO	NO	NO	NO
4	Haiges et al[6]	2017	Pale tumor cells arranged in nests and trabecula with delicate network capillary vessels. 3N+/3N	No	Yes	7/40HFP	NO	NO	NO	NO
7	Cole et al[7]	2021	Epithelioid cell tumor with marked atypia and hypercellularity	No	Yes	4/10 HPF	NO	NO	NO	NO
3	Cornell et al[9]	2022	Nests and trabecule, thin-walled capillary, fine granular to clear cytoplas,high-grade cellular atypia	No	Yes	7/10HPF	yes	NO	NO	NO
5	Neumann et al[10]	2022	Sheets of large, hyperchromatic cells with clumped chromatin, macronucleoli, and bizarre nuclear forms	No	Yes	up to 22/2 mm2	yes	yes	yes	NO
6	Cohen et al[8]	2022	sheets celles with thin-walled capillary, fine granular to clear cytoplasm	No	Yes	3/ 10 HPF	NO	yes	NO	NO
8	Present case	2023	Irregular nests and nodules with numerous branching capillaries. Cells had abundant clear cytoplasm and polymorphic nuclei with prominent nucleoli	No	Yes	6/ 2mm^2	yes	yes	NO	NO

Abbreviation: HPF, high power field.

Table 3. Immunohistochemical features of reported primary cutaneous malignant PEComa cases.

CASE	REFERENCE	YEAR	MELAN A	HMB-45	MIT-F	S-100 PROTEIN	SOX10	SMA	DESMIN	H-CALDESMONE	CD10	CD68	VIMENTIN	TFE3	EPITHELIAL MARKERS	NEUROENDOCRINE MARKERS	OTHERS
1	Calder et al[4]	2008	positive	positive	ND	negative	ND	positive	ND	ND	ND	ND	ND	ND	negative	ND	CD45-, PLAP-
2	Greveling et al[5]	2013	positive	positive	positive	positive	ND	positive	negative	negative	positive	positive	positive	ND	negative	negative	Tyrosinase-
4	Haiges et al[6]	2017	negative	positive	negative	negative	negative	negative	ND	ND	positive	ND	ND	negative	ND	ND	
7	Cole et al[7]	2021	ND	positive	positive	ND	ND	ND	ND	ND	positive	positive	ND	negative	ND	ND	PRAME-
3	Cornell et al[9]	2022	negative	negative	positive	ND	negative	negative	negative	ND	ND	ND	ND		negative	ND	PAX-8-
5	Neumann et al[10]	2022	negative	positive	negative	negative	negative	negative	negative	positive	ND	ND	positive	positive	ND	ND	
6	Cohen et al[8]	2022	negative	positive	ND	negative	negative	negative	negative	positive	ND	ND	ND	positive	ND	ND	
8	Present case	2023	positive	negative	ND	negative	ND	positive	negative	negative	positive	positive	positive	negative	negative	negative	CD45-, Myogenin-

Abbreviation: ND, not done.

Llamas-Velasco et al.,[15] and FISH assay for TFE3 rearrangement yielded negative results in this same study. However, 2 primary cutaneous malignant PEComas have previously reported, they showed TFE3 positivity (2/6) (Table 3).

Genetically, primary cutaneous malignant PEComas have a different molecular signature than their systemic counterparts. Loss of function in tuberous sclerosis complex 1 (TSC1) or 2 (TSC2) in systemic PEComas cause an activation of the mTOR pathway; however, primary cutaneous malignant PEComas are unrelated to tuberous sclerosis complex and show overactivation of the mTOR pathway by a different mechanism. So overexpression of 4EBP1, which is an effector protein in the mTOR pathway, supports mTOR overactivation independent of TSC1 or TSC2 mutations in primary cutaneous malignant PEComas.[16]

Given the rarity of primary cutaneous PEComas, treatment options and prognostic factors are not well established. In all published cases of primary cutaneous PEComas, radical surgery with free margins was the gold standard treatment followed by radiotherapy in 2 patients.[7,8] Some authors report that treatment with mTOR inhibitor (nab-sirolimus) seems to be useful in the treatment of cases with mTOR overactivation.

Follow-up data were available for 7 of 8 patients and ranged from 6 to 24 months with a mean of 10 months. All of these reported primary cutaneous malignant PEComas showed no evidence of metastatic disease and none of the patients presented recurrence after therapy (Table 1). Our patient has followed in oncology after the surgical excision and adjuvant thetapy, and no evidence of recurrence or metastasis have been revealed to date.

Conclusions

This case highlights an additional case of a primary cutaneous malignant PEComa, which clinically seemed an aggressive skin malignancy. On histologic analysis, we found a dermal clear cell epithelioïd neoplasm with marked atypia, hypercellularity, and high mitotic activity. On immunohistochemistry, tumor cells co-expressed muscle and melanocytic markers, they expressed also CD10. Therefore, cutaneous tumors that express CD10 should not only raise the possibility of metastasis from renal cell carcinoma but for a precise diagnosis, a wide immunohistochemical analysis with a panel of multiple antibodies is required. Diagnosing primary cutaneous PEComas is challenging given their rarity, on the 1 hand, pathologists have to bring to mind this diagnosis facing a dermal clear-cell tumor, and on the other hand, they should argue for malignancy based on the features described above.

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Author Contributions

Layla Tahiri Elousrouti and Laila Chbani did the histological and imunohistological diagnosis, conceived the study, participated in its design and coordination, and drafted the manuscript. N Hammas, A Mouadden, and I Fadlalalh participated in pathological process. S elhitmi, S Eloudi and FZ Mernissi did clinical examination and biopsy specimen. M Elidrissi resected chirugically the tumor. S Arifi and T Bouhafa indicated the systemic treatment and radiation.

Consent

Written informed consent has been obtained from the patient to publish this paper.

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